Supplementary tables

Animal models and pathogenesis of thoracic aortic aneurysm

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**Table S1**. Recent studies employing BAPN-induced TAA models in rodents

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species, strain | Sex | Age(w) | BAPNdose | Inductiontime, w | Aortic diameter Increase | TAARate, % | Rupt.rate,% | Dissection | Ref |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | NR | Yes | [1] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | NR | Yes | [2] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | 45.7 | Yes | [3] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | 73.3 | 46.7 | Yes | [4] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes  | NR | <80 | Yes | [5] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | NR | NR | 80 | Yes | [6] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | 23.3 | Yes | [7] |
| Mice, C57BL/6 | NR | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | 14.3 | Yes  | [8] |
| Mice, C57BL/6 | NR | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | >50 | Yes | [9] |
| Mice, C57BL/10 | M | 3 | 0.5 g/kg/d in DW | 4 w | NR | NR | <60 | Yes | [10] |
| Mice, C57BL/6 | M | 3 | 0.5 g/kg/d in DW | 4 w | Yes | NR | 11 | Yes | [11] |
| Mice, C57BL/6 | M | 3 | 0.5 g/kg/d in DW | 4 w | NR | NR | 12.5 | Yes | [12] |
| Mice, C57BL/6 | M & F | 3 | 0.5 g/kg/d in DW | 1, 2, 3 or 4 w | Yes | NR | 86.7 (M)58.8 (F) | Yes | [13] |
| Mice, C57BL/6 | M | 3 | 0.4 g/100 g diet | 18 d | Yes | NR | NR | Yes | [14] |
| Mice, C57BL/6 | M | 3 | 6 g/L in DW | 4 w | Yes) | 83.3 | NR | Yes | [15] |
| Mice, C57BL/6 | NR | 3 | 2.5g/L in DW | 4 w | Yes | 42.9 | 42.9 | Yes | [16] |
| Mice, C57BL/6 SJL | M | 3-4 | 3 g/L in DW | 26 w | Yes | 50 | 15.2 | NR | [17] |
| Mice, C57BL/6 | M | 3 | 1 g/L in DW | 6 w | Yes | NR | 66 | NR | [18] |
| Rats, SD | M | 3 | 1 g/kg/d, intragastric | 4 w | Yes | 16.7 | 0 | NR | [19] |

BAPN, β-aminopropionitrile; d, day; DR, drink water; F, female; M, male; NR, not reported; Rupt., rupture; SD, Sprague-Dawley; w, weeks.

**Tablel S2.** Recent studies employing rodent TAA models induced by angiotensin II infusion

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species | Strain | Sex | Age, W | Dose,μg/kg per min | Time, W | TAA rate, % | Rupture rate, % | Dissectionrate, % | Ref |
| Mice | ApoE−/− | M | 12 | 1  | 4 | NR | NR | NR | [20] |
| Mice | ApoE−/− | M | 8-10 | 1  | 4 | NR | NR | NR | [21] |
| Mice | ApoE−/− | M | adult | NR | NR | NR | NR | NR | [22] |
| Mice | Wild typeandPlce1−/− | M&F | 10 to 12 | 1 | 4 | 80% | 43%  | NR | [23] |
| Mice | Wild typeandLoxl4−/− | M | 14 or 20  | 1 or 1.5  | 4 | 28.6% | NR | NR | [24] |
| Mice | Wild type andTfam−/− | M | 4-5 | 1 | 4 | 100% | 70% | 70% | [25] |
| Rat | SD | F | 8 | 1.2 | 4 | 85% | NR | NR | [26] |

ApoE−/−, apolipoprotein E-deficient; F, female; Loxl4−/−, lysyl oxidase (LOX)-like proteins 4-deficient; M, male;NR, not reported; Plce1−/−, phospholipase Cε-insufficient; SD, Sprague-Dawley; Tfam−/−, mitochondrial transcription factor A-deficient;W, week.

**Table S3**: Recent studies employing elastase-induced TAA models in rodents

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species,strain | Sex | Age, w | PPE site | PPE dose | PPE time,min | Experimental period, w | TAA rate, % | Rupture rate, % | Dissection rate, % | Ref |
| Mice,C57BL/6 | M | 8-12 | ATA & arch | 15 µL | 5 or10 | 1-4 | 43 or71 | 0 or 18 | NR | [27] |
| Mice,C57BL/6 | M | 8-12 | DTA | NR | 4 | 2 | NR | NR | NR | [28] |
| Mice,C57BL/6 | M | 8-10 | DTA | 12 μL | 3 | 2 | 100 | NR | NR | [29] |
| Rats, SD | F | 12 | DTA | NR | 15-20 | NR | NR | NR | NR | [30] |

ATA, ascending thoracic aorta; DTA, descending thoracic aorta; NR, not reported; PPE, porcine pancreatic elastase; SD, Sprague-Dawley; TAA, thoracic aortic aneurysm; w, week.

**Table S4**. Recent studies employing CaCl2-induced TAA models in rodents

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species, strain | Sex | Age | CaCl2Conc. | CaCl2time, min | Exp. Duration,Weeks | Aortic diameter increase | TAARate, % | Rupt.rate,% | Dissection rate, %(or yes/no) | Ref |
| Mice,129/SvE  | M&F | NR | 0.5 M | 15 | 4 | 25% | NR | NR | NR | [31] |
| Mice,C57BL/6 | M&F | 10 w | 0.5 M | 15 | 4, 8, 16 | 59.5% 4 w64.3% 8 w62.9% 16 w | 90% | NR | NR | [32] |
| Rats, WS | M | NR | 0.5 M | 15 | 4 | 18%  | NR | NR | NR | [33] |
| Rats, SD  | NR | NR | 0.5 M | 15 | 4 | NR | NR | NR | NR | [34] |

CalCl2, calcium chloride; Conc., concentration; Exp., experimental; F, female; M, male; NR, not reported; Ref, reference; Rupt., rupture; SD, Sprague-Dawley; TAA, thoracic aortic aneurysm; w, week; WS, Wistar.

**Table S5.** Recent studies employing combination of BAPN and angiotensin II-induced TAA models in rodents

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species | Strain | Sex | Age,  W | BAPN | Angiotensin II | TAA rate, % | TAA diameter increase | Rupture | Dissection  | Reference |
|  |  |  |  | Dose | Time, days | Route | Dose,μg/kg/min | Time, day |  |  |  |  |  |
| Mice | C57BL/6 | M | 3 | 0.15 μg/kg/d | 28 | i.p. | 1 | 3 | 40 | Yes | Yes | NR | [35] |
|  |  |  |  |  |  |  |  | 28 | 73 |  |  |  |  |
| Mice | C57BL/6 | M & F | 10–15 | 0.2% | 28 | DW | 1 | 25 (3 days after initiation of BAPN) | NR | Yes  | Yes | NR | [36] |
| Mice | C57BL/6, or FVB | M | 3 | 0.4% | 28 | Diet | 1 | 1 | NR | NR | Yes | Yes,100% | [37] |
| Mice | C57BL/6 | M | 3 | 1 μg/kg/d | 28 | DR | 1 | 2 | 25 | Yes | Yes | Yes | [38] |

BAPN, β-aminopropionitrile; DR, drinking water; i.p., intraperitoneal;NR, not reported; TAA, thoracic aortic aneurysm; W, week;

**Table S6: Recent studies investigating potent therapeutic target against TAA in animal models**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TAA induction | Animals | Intervention | TAA incidence | Aortic diameter | Rupture | Mechanism | Targets | Ref |
| Inflammation |
| BAPN | C57BL/6 mice | Dexamethasone | ↓ | ↓ | NR | ↓ Macrophage and neutrophil infiltration ↓ Apoptosis of VSMC ↓ MMP 2/9↓ ECM degradation  | InflammationApoptosisECM degradation | [3] |
| Genetic | VSMC-specific Tgfbr2- deficient mice | Dexamethasone | ↓  | ↓  | NR | ↓ CCL8↓ Macrophage infiltration↓ MMP2↓ NF-*κ*B  | Inflammation | [39] |
| Genetic | Fbn1C1039G/+ mice | Folic acid | ↓ | ↓ | NR | ↓ NOX4 ↓ Superoxide production↓ Elastin fiber fragmentation | InflammationECM degradation | [40] |
| BAPN | C57BL/6 | Metformin | ↔ | ↓  |  ↔ | ↓ Inflammation↓ Elastin breakage | InflammationECM degradation | [15] |
|  BAPN | C57BL/6 mice | Melatonin | ↓ | ↓ | ↓ | ↑ SIRT1 signalling↓ Macrophage infiltration↓ MMP2, MMP9 ↓ Reactive oxygen species↓ VSMC loss  | InflammationOxidative stress | [7] |
| Genetic | Fbn1mgR/mgR | Digoxin | NR |  ↓ | NR | ↑ miR-122, ↓ CCL2 ↓ MMP12↓ Elastin fragmentation | InflammationECM degradation | [41] |
| BAPN | C57BL/6 | Oltipraz (Nrf activator) |  ↓ |  ↓ |  ↓ | ↓ Apoptosis ↓ Macrophage infiltration↓ MMP | InflammationApoptosis | [9] |
| BAPN | C57BL/6 mice | TEPP-46 (activator of glycolytic enzyme pyruvate kinase M2) | ↓ | ↓ | ↓ | ↓ Inflammatory cells infiltration↓ ROS↓ Caspase 1↓ VSMCs loss  | InflammationOxidative stressApoptosis | [8] |
| CaCl2  | Sprague-Dawley rats | Cordycepin, (an anti-inflammatory and antioxidant compound) | ↓ | ↓ | NR | ↓ VEGF ↓ IL-6, TNF-α and IL-1β ↓ ROS↓ Caspase 3/9 and apoptosis | InflammationOxidative stressApoptosis | [34] |
| BAPN | C57Bl/6 mice | Myriocin  | ↓  | NR | ↓ | ↓ Inflammation (IL-1β, TNF-α, and IL-6) | Inflammation | [12] |
| BAPN+AngII | C57Bl/6 mice | Senkyunolide I | ↓ | ↓ | ↓ | ↓ Inflammation↓ ROS↓ Apoptosis↑ Elastin integrity | InflammationOxidative stressApoptosisECM degradation | [42] |
| Ang II,BAPN,Genetic | Mice | Allopurinol | ↓ | ↓ | ↓ | ↓ Uric acid↓ Inflammation | Inflammation | [43] |
| Ang II | ApoE−/− mice | Angiotensin 1-7 | ↓ | ↓ | NR | ↓ Inflammation↓ MMP2, 9↑ Elastin integrity | Inflammation | [21] |
| BAPN | C57BL/10 mice | Macrophage inhibitors Ki20227, mLR12 | ↓ | ↓ | ↓ | ↓ Macrophage infiltration↓ Inflammation↓ MMP 2&9 | Inflammation | [10] |
| BAPN TACGenetic  | C57B/L6 miceFbn1C1041G/+ mice |  Angiogenic factor with G-patch and FHA domains 1 | ↓ | ↓ | NR | ↓TGF-β and ERK1/2 ↓ Inflammation | TGFβInflammation | [16] |
| BAPN | C57/BL6 SJL | Moderate aerobic exercise | ↓ | ↓ | ↓ | ↓ TGF-β pathway ↓ Inflammatory markers↑ Elastogenesis | InflammationECM formation | [17] |
| Genetic  | Fbn1C1039G/+ mice  | Antisense oligonucleotide against angiotensinogen | ↓ | ↓ | NA | ↓ Inflammatory gene expression↓ Elastin fragmentation | InflammationECM degradation | [44] |
| Elastase  | C57Bl/6 mice | Administration of mesenchymal stem cells  | ↓ | ↓ | NR | ↓ T cell, neutrophil and macrophage infiltration ↓ Proinflammatory cytokines↑ Anti-inflammatory IL-10 ↓ Elastic degradation  | InflammationECM degradation | [28] |
| Apoptosis |
| BAPN | SD rats | Methamphetamine | ↑ | ↑ | ↑ | ↑ MMP 2&9 ↑ Elastin breakage↑ VSMC apoptosis | ApoptosisECM degradation | [19] |
| BAPN | C57BL/6 Mice | Ciprofloxacin (antibiotic) | ↑ | ↑ | ↑ | ↑ Apoptosis↑ MMP9 ↑ ECM degradation | ApoptosisECM degradation | [2] |
| BAPN | C57BL6 mice | Diesel exhaust particulate | ↑ | ↑ | ↔ | ↑ apoptosis↑ BAX/Bcl2↑ Caspase 3/cleaved Cas3 | Apoptosis | [45] |
| BAPN | C57BL/6 mice | Dexamethasone | ↓ | ↓ | NR | ↓ Macrophage and neutrophil infiltration ↓ Apoptosis of VSMC ↓ MMP 2/9↓ ECM degradation  | InflammationApoptosisECM degradation | [3] |
| BAPN | C57BL/6 mice | TEPP-46 (activator of glycolytic enzyme pyruvate kinase M2) | ↓ | ↓ | ↓ | ↓ Inflammatory cells infiltration↓ ROS↓ Caspase 1↓ VSMCs loss  | InflammationOxidative stressApoptosis | [8] |
| CaCl2  | SD rats | Cordycepin, (an anti-inflammatory and antioxidant compound) | ↓ | ↓ | NR | ↓ VEGF ↓ IL-6, TNF-α and IL-1β ↓ ROS↓ Caspase 3/9 and apoptosis | InflammationOxidative stressApoptosis | [34] |
| Genetic | Fbn1C1041G/+ mice  | Nitro-oleic acid | ↓ | ↓ | NR | ↓ ERK1/2↓ Smad2 ↑ NF-κB↓ MMP2↓ Apoptosis | TGFβInflammationApoptosis | [46] |
| BAPN | C57BL/6 | Oltipraz (Nrf activator) |  ↓ |  ↓ |  ↓ | ↓ Apoptosis ↓ Macrophage infiltration↓ MMP | InflammationApoptosis | [9] |
| ECM degradation |
| Genetic | Fbn1C1039G/+ mice | Rapamycin | ↓ | ↓ | NR | ↓miR-126-3p and subsequent ERK1/2 signalling↓MMP-9 expression↓Elastin degradation | ECM degradation | [47] |
| BAPN  | C57BL/6 mice | Rapamycin | ↓ | ↓ | ↔ | ↓ mTOR pathway ↓ Macrophage and neutrophil infiltration↓ MMP9↓ Elastic fiber fragmentation | mTORECM degradation | [4] |
| Genetic | Mice deficient in hamartin, an inhibitor of mTOR  | Rapamycin | ↓ | NR | NR | ↓ mTOR activation ↓ Elastic fiber fragmentation | mTORECM degradation | [48] |
| Genetic | Fbln4SMKO C57BL/6 mice | Dabigatran (thrombin inhibitor)Rivaroxaban (factor Xa inhibitor) | ↓  | NR | NR | ↓ Protease activated receptor 1 | ECM | [49] |
| Genetic | Fbn1C1039G/+ mice | ODQ (sGC inhibitor)KT5823 (PRKG inhibitor)PRKG1 silencing | NR | ↓ | NR | ↓Elastin fiber fragmentation  | NO–sGC–PRKGECM degradation | [50] |
| Genetic | Fbn1mgR/mgR mice | DAPT (Notch inhibitor) | NR | ↓  | ↓  | ↓ Elastin degradation | ECM degradation | [51] |
| Genetic | Fbn1C1039G/+ mice | HIPK2 Inhibitor BT173  | ↓ | ↓ | ↓ | ↓ Elastin fiber fragmentation ↓Collagen accumulation | ECM degradation | [52] |
| Genetic | Fbn1C1039G/+ mice | Flutamide (androgen receptor blocker) | NR | ↓  | NR | ↓ Erk1/2, Smad2 ↓ MMP2 ↓ Elastin fiber fragmentation | TGFβ ECM degradation | [53] |
| BAPN | C57BL/6 mice | Crocin (MMP inhibitor) | ↓ | ↓ | ↓ | ↓ MMP activity↓ Elastin degradation | ECM degradation | [5] |
| Genetic | Fbn1C1039G/+ mice | Nicotinamide riboside (NAD+ precursor to normalize mitochondrial function) | NR | ↓ | NR | ↑ Mitochondrial dysfunction↓ Elastin fiber fragmentation | Mitochondrial functionECM degradation | [25] |
| Ang II  | SD rats  | AgomiR-22 | NR | ↓ | NR | ↓ MMP-9↑ ECM integrity | ECM degradation | [26] |
| CaCl2 | C57BL/6 mice | miR-133a overexpression  | ↓ | ↓ | NR | ↓ Pro – protein convertase furin↓ Elastic fiber fragmentation | ECM degradation | [32] |
| Miscellaneous |
| Genetic | Fbn1C1039G/+ mice | Vitamin B | ↓ | ↓ | NR | ↑Smad4↑ collagen maturation | Collagen maturation | [54] |
| Genetic | Fbn1mgR/mgR mice | baclofen (GABAB receptor agonist) | ↓  | ↓  | ↓  | ↑ muscle contractility↑ aortic wall microarchitecture | Contractility | [55] |
| TGFβ inhibition  | Zebrafish | TGFβ antagonist LY364947 | ↑ | ↑ | NR | ↓ pSmad3 | TGFβ | [56] |

↔, no effect; ↑, increase; ↓, decrease; Ang II, angiotensin II; ApoE−/−, apolipoprotein E-deficient; BAPN, β-aminopropionitrile; Bcl2, B-cell lymphoma 2; CaCl2, calcium chloride; CCL, chemokine (C-C motif) ligand; ECM, extracellular matrix; Erk, extracellular signal–regulated kinase; Fbn1, fibrillin-1; Fbln4, fibulin-4; Fbln4SMKO, smooth muscle-specific fibulin-4 knockout; GABA, gamma-aminobutyric acid; HIPK2, homeodomain-interacting protein kinase 2; IL, interleukin; MMP, matrix metalloproteinases; mTOR, mammalian target of rapamycin; NF-κB, Nuclear Factor Kappa B;NO, nitirc oxide; NR, not reported; Nrf: nuclear factor erythroid 2-related factor 2; Ltbp, latent TGFβ-binding protein; NOX4, NADPH oxidase 4;PRKG1, type 1 cGMP-dependent protein kinase; Ref, reference; ROS, reactive oxygen species; SD, Sprague-Dawley; sGC, soluble guanylate cyclase; SIRT1, sirtuin 1; Smad, suppressor of mothers against decapentaplegic; TGFβ, transforming growth factor-beta; Tgfbr2, TGFβ type 2receptor; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells.

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